UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/464,303	12/15/1999	GREGORY L. STAHL	B0801/7156	7348

7590 07/05/2006

HELEN C LOCKHART
WOLF GREENFIELD & SACKS P C
600 ATLANTIC AVENUE
BOSTON, MA 02210

EXAMINER	
VANDERVEGT, FRANCOIS P	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 07/05/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/464,303	STAHL ET AL.	
	Examiner	Art Unit	
	F. Pierre VanderVegt	1644	.

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-67 and 69-93* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *80-86* is/are allowed.

6)☒ Claim(s) *63-68,72-79 and 87-93* is/are rejected.

7)☒ Claim(s) *69-71* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This application claims the benefit of the filing date of provisional application 60/112,390.

Claims 1-62, 68 have been canceled.

New claims 86-93 have been added.

Claims 63-67 and 69-93 are currently pending and are the subject of examination in the present Office Action.

In view of Applicant's amendment filed April 17, 2006, only the following grounds of rejection are maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 63-67, 72-79 and 87-93 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

It was previously stated: "The claims are broadly drawn to an antibody or fragment thereof that binds to human MBL wherein the antibody comprises a CDR3 region of one of 3 deposited monoclonal antibodies. Claim 75 recites the further limitation that the claimed antibody also comprises a CDR2 region from one of the monoclonal antibodies, but is silent about the presence of a CDR1 region. Claim 77 recites the further limitation that the claimed antibody also comprises a CDR1 region from one of the monoclonal antibodies, but is silent about the presence of a CDR2 region. The claims do not require that the CDR regions are obtained from the same antibody or from the same chain of the antibody. The specification does not disclose the amino acid sequence of any of the monoclonal antibodies or of any portion of the monoclonal antibodies.

The CDR3 region of an immunoglobulin molecule is only about 8-9 amino acid residues in length. However, based upon a 9 amino acid segment (which has not been sequenced), the instant claims broadly recite any antibody, or antigen-binding fragment thereof, that binds to mannose binding lectin. The specification does not teach the individual isolation of the CDR1, CDR 2 or CDR3 region of the heavy or light chain of any of the three disclosed deposited monoclonal antibodies. Furthermore the specification does not teach that any of the six CDR regions from any of the three disclosed deposited antibodies are capable of binding mannose-binding lectin on their own. The specification discloses only the ability of the monoclonal antibodies 3F8, 2A9 and hMBL1.2 to bind mannose-binding lectin.

Vas-Cath Inc. v. Mahurkar ((CAFC, 1991) 19 USPQ2d 1111), clearly states that "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in

possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See *Vas-Cath* at page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see *Vas-Cath* at page 1115).

Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody 3F8, and that is the monoclonal antibody 3F8 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12621. Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody hMBL1.2, and that is the monoclonal antibody hMBL1.2 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12619. Applicant's deposit demonstrates only possession of a single monoclonal antibody possessing the CDRs of monoclonal antibody 2A9, and that is the monoclonal antibody 2A9 produced by the hybridoma cell line deposited under ATCC Accession No. HB-12620.

Therefore, despite Applicant's contention that possession of the deposited monoclonal antibodies as a whole molecule entitles Applicant to consideration as being in possession of the individual CDR regions contained in those antibodies, a lack of a description of the actual structure of the individual CDR regions and a lack of a description of the actual binding properties of the individual CDR regions demonstrates instead that Applicant was not in possession of those individual CDRs as mannose binding ligands as part of any other antibody or antigen binding fragment thereof. Applicant has demonstrated only the possession of the deposited monoclonal antibodies and antigen binding fragments thereof.

Applicant's citation in the response of the work of others that CDR3 regions of some antibodies are able to bind antigen as an individual peptide (without CDR1 or CDR2 involvement) is not pertinent to the instant case. The cited references show only the work of others demonstrating specifically that the CDR3 regions of their disclosed antibodies are able to bind antigen. The references do not, however, speak to the ability of the CDR3 regions of 3F8, 2A9 and hMBL1.2 to specifically bind mannose-binding ligand and neither does the instant specification. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, ((CAFC, 1993) 25 USPQ 2d 1601) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*,((CAFC, 1991) 18 USPQ2d 1016).

Applicant's arguments filed April 17, 2006 have been fully considered but they are not persuasive.

Applicant continues to argue that the mixing of CDR regions between the three disclosed monoclonal antibodies or including only a single CDR from one of the disclosed monoclonal antibodies is adequately described in the instant specification. The Examiner continues to disagree with this position. While a single isolated CDR may bind to an antigen, there is no description of using a CDR from one of the antibodies with any of the other antibodies or with up to 5 CDRs from an undisclosed antibody. EACH of the CDR regions in an antibody molecule contributes to the binding properties of that monoclonal antibody and affects the ability of the other CDRs to bind. Proteins, including immunoglobulins, are 3-dimensional molecules with conformational considerations that affect their interaction with other molecules, such as a target epitope. If such conformational considerations were not a concern, then there would be no need for an artisan to reshape the framework regions of an antibody to optimize the binding of the chimeric antibody molecule.

As an example, let us consider only mixing the CDRs from the disclosed HB-12621, HB-12620 and HB-12619 monoclonal antibodies. The heavy chain CDR3 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The heavy chain CDR2 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The heavy chain CDR1 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The same reasoning may be applied to the CDRs of the light chain. If an artisan were to combine the HC CDR3 of HB-12621 in a reshaped antibody with the HC CDR2 of HB12620, the CDRs may interfere with one another's binding to an MBL epitope or the contact points of the two CDRs may not be close enough together for them to both bind MBL.

Each monoclonal antibody has its own binding characteristics and those characteristics are contributed by all 6 CDR regions of that antibody because the contact points of those 6 CDRs are conformationally compatible with one another to allow binding of the antibody molecule to the target epitope. Replacing one or more of those CDR contact points with a CDR contact point from a different antibody is likely to disturb the conformational balance of the monoclonal.

New claims 87-93 are included, while base claim 83 is not, because base claim 83 reads solely upon an antigen-binding fragment of one of the three disclosed monoclonal antibodies, while dependent claims 87-93 again introduce and invite mixing of CDR regions from different antibodies.

2. Claims 63-68, 72-79 and 87-93 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an antibody produced by the hybridoma cell lines 2A9, 3F8 and hMBL1.2 and antigen-binding fragments thereof does not reasonably provide enablement for the broader recitation of any antibody or antigen binding fragment thereof comprising an MBL CDR3 region extracted from 2A9, 3F8 or hMBL1.2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It was previously stated: "Factors to be considered in determining whether undue experimentation is required are summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to an antibody or fragment thereof that binds to human MBL wherein the antibody comprises a CDR3 region of one of 3 deposited monoclonal antibodies. Claim 75 recites the further limitation that the claimed antibody also comprises a CDR2 region from one of the monoclonal antibodies, but is silent about the presence of a CDR1 region. Claim 77 recites the further limitation that the claimed antibody also comprises a CDR1 region from one of the monoclonal

antibodies, but is silent about the presence of a CDR2 region. The claims do not require that the CDR regions are obtained from the same antibody or from the same chain of the antibody. The specification does not disclose the amino acid sequence of any of the monoclonal antibodies or of any portion of the monoclonal antibodies.

The CDR3 region of an immunoglobulin molecule is only about 8-9 amino acid residues in length. However, based upon a 9 amino acid segment (which has not been sequenced), the instant claims broadly recite any antibody, or antigen-binding fragment thereof, that binds to mannose binding lectin. The specification does not teach the individual isolation of the CDR1, CDR 2 or CDR3 region of the heavy or light chain of any of the three disclosed deposited monoclonal antibodies. Furthermore the specification does not teach that any of the six CDR regions from any of the three disclosed deposited antibodies are capable of binding mannose-binding lectin on their own. The specification discloses only the ability of the monoclonal antibodies 3F8, 2A9 and hMBL1.2 to bind mannose-binding lectin.

In order to engineer other antibodies comprising the CDR regions of one of the instantly disclosed deposited antibodies there is a requirement for sequence information for the CDR regions themselves. Sequence information is also needed for the framework regions flanking the CDRs in order to graft the CDR into an immunoglobulin molecule and to properly orient the CDR for antigen binding. However, the specification fails to provide any sequence information whatsoever regarding the CDR and framework regions of the heavy or light chains of monoclonal antibodies 3F8, 2A9 and hMBL1.2.

Janeway et al. (Immunobiology 4th Edition [1999] page87; of record) teaches that the CDR1, CDR2 and CDR3 regions of the heavy and light chains determine antigen specificity of an antibody. Applicant has argued, in regard to the Janeway reference, that CDR1 and CDR2 "might further contribute partially to binding," in asserting that Janeway stresses the importance of CDR3 to binding. In fact, Janeway treats CDR1, CDR2, and CDR3 equally and does not emphasize any one over the others. Further, Janeway clearly shows that not only are all three CDRs important, but the intervening framework sequences contribute significantly to the 3-dimensional relationship of CDR1, CDR2, and CDR3 to one another, orienting the CDRs properly for forming the binding site. Applicant's further contention that peptides comprising the CDR3, in the form of F(ab) and F(ab')$_2$ fragments, have been shown bind MBL is not convincing to support the broad recitation of the claims, as applicant is reminded that F(ab) and F(ab')$_2$ fragments also comprise CDR1 and CDR2 regions and comprise both the heavy chain variable region and the light chain variable region, meaning that the Ab fragments have CDR1, CDR2, and CDR3 contributions from both chains.

Applicant continues to assert that articles by Laune, Monnet, Taub and Igarashi (citations on page 9 of response filed April 24, 2004) support the argument that peptides comprising the CRD3 would be able to bind MBL. However, each of the references teaches that CDR-containing fragments of the antibodies from which they are derived are capable of binding to the target antigen The cited references show only the work of others demonstrating specifically that the CDR3 regions of their disclosed antibodies are able to bind antigen. The references do not, however, speak to the ability of the CDR3 regions of 3F8, 2A9 and hMBL1.2 to specifically bind mannose-binding ligand and neither does the instant specification.

In view of the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take undue trials and errors to practice the claimed invention and the statute does not sanction this."

Similar to the situation *supra*, Applicant continues to argue that the mixing of CDR regions between the three disclosed monoclonal antibodies or including only a single CDR from one of the disclosed monoclonal antibodies is adequately enabled by the instant specification. The Examiner continues to disagree with this position. While a single isolated CDR may bind to an antigen, there is no

description of using a CDR from one of the antibodies with any of the other antibodies or with up to 5 CDRs from an undisclosed antibody. EACH of the CDR regions in an antibody molecule contributes to the binding properties of that monoclonal antibody and affects the ability of the other CDRs to bind. Proteins, including immunoglobulins, are 3-dimensional molecules with conformational considerations that affect their interaction with other molecules, such as a target epitope. If such conformational considerations were not a concern, then there would be no need for an artisan to reshape the framework regions of an antibody to optimize the binding of the chimeric antibody molecule.

As an example, let us consider only mixing the CDRs from the disclosed HB-12621, HB-12620 and HB-12619 monoclonal antibodies. The heavy chain CDR3 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The heavy chain CDR2 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The heavy chain CDR1 regions of the three monoclonal antibodies may not bind to the exact same point in an epitope of MBL. The same reasoning may be applied to the CDRs of the light chain. If an artisan were to combine the HC CDR3 of HB-12621 in a reshaped antibody with the HC CDR2 of HB12620, the CDRs may interfere with one another's binding to an MBL epitope or the contact points of the two CDRs may not be close enough together for them to both bind MBL.

Each monoclonal antibody has its own binding characteristics and those characteristics are contributed by all 6 CDR regions of that antibody because the contact points of those 6 CDRs are conformationally compatible with one another to allow binding of the antibody molecule to the target epitope. Replacing one or more of those CDR contact points with a CDR contact point from a different antibody is likely to disturb the conformational balance of the monoclonal.

New claims 87-93 are included, while base claim 83 is not, because base claim 83 reads solely upon an antigen-binding fragment of one of the three disclosed monoclonal antibodies, while dependent claims 87-93 again introduce and invite mixing of CDR regions from different antibodies.

Allowable Subject Matter

3. Claims 80-86 are allowed.

4. Claims 69-71 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to F. Pierre VanderVegt whose telephone number is (571) 272-0852. The examiner can normally be reached on M-Th 6:30-4:00 and Alternate Fridays 6:30-3:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

F. Pierre VanderVegt, Ph.D.
Patent Examiner
June 26, 2006

DAVID SAUNDERS
PRIMARY EXAMINER
ART UNIT ~~182~~ 1644